This is an update of the ASRM Zika virus guidance for providers that addresses the care of non-pregnant patients desiring pregnancy, originally released in September 2016 and updated in August 2018. This revised document reflects the changes that the CDC has made on its Blood and Tissue Safety webpage to more clearly communicate epidemiological information about the risk of Zika virus infection outside of the U.S., with links to the updated CDC webpages. In addition, the most recent information about Zika virus infection risk within the U.S. is included. This updated ASRM guidance specifically addresses Zika virus infection issues and concerns of individuals and couples undergoing assisted reproductive technologies (ART), including those with frozen gametes and embryos. These individuals differ from the general population because attempting pregnancy via ART requires the active role of medical providers and the timing is discretionary. As a result, deliberate efforts can be made to minimize the risk of having a Zika virus-infected pregnancy for couples who either live in or plan to visit areas where Zika virus infections are known to occur.

1. **Reproductive healthcare providers should perform preconception counseling that includes a discussion of Zika virus diagnostic challenges and unmitigated risks based on the most current available data and national and regional guidance.**
   - In areas of Zika virus transmission, healthcare providers should discuss strategies to prevent congenital Zika virus infection and unintended pregnancy, including use of the most effective contraceptive methods. In addition, as Zika has been shown to be transmitted sexually, patients should be counseled that correct and consistent use of condoms reduces the risk of sexually transmitted infections.
   - Discussions about pregnancy timing should be individualized and should include information about the signs and symptoms of Zika virus disease and the potential adverse outcomes associated with Zika virus infection in pregnancy, even in asymptomatic infected women. Preliminary data from the CDC reported that Zika virus-associated birth defects occurred in 10% of pregnancies with laboratory-confirmed Zika virus infection, and in 15% of pregnancies where Zika virus infection occurred during the first trimester.  
   - The CDC reported that of 1,450 babies born in the U.S. Territories after confirmed or possible Zika virus infection during pregnancy, one in seven evaluated had a neurodevelopmental condition that could possibly be related to Zika virus infection. Most children did not have all the recommended evaluations; thus, additional anomalies might not have been identified.  
   - Currently, although there are limited data, there is no evidence that Zika virus will cause congenital infection in pregnancies initiated after the resolution of maternal Zika viremia.
   - Male and female partners who become infected should avoid intimate sexual contact or use condoms during the time that they delay attempts of pregnancy. Transmission through vaginal and anal sex has been demonstrated. Animal studies suggest that an enhanced viral dissemination during sexual transmission while pregnant may pose a greater risk than the subcutaneous transmission from a mosquito bite. Data on transmission through oral sex and the sharing of sex toys are still lacking.
   - If the male or female partner of a pregnant woman becomes infected or tests positive for Zika virus, he or she should avoid intimate sexual contact as described above or use condoms for the duration of the pregnancy.

2. **Infertility treatment centers caring for patients at risk of infection during the course of treatment or subsequent pregnancy should develop strategies to mitigate the risk of viral transmission to the patient and the fetus. Standard infection control precautions should protect healthcare workers.**
   - Strategies should incorporate sufficient counseling about the challenges of interpreting test results, even from direct viral RNA testing, the Zika virus nucleic acid test (NAT). For instance, Zika RNA may persist for longer durations in bodily fluids, such as semen, and for shorter periods of time in serum. Whether to be tested or not must take into consideration the declining prevalence of Zika, the possibility of false-positive and false-negative
results, and the chance of becoming infected with Zika after testing, and this should involve a shared patient-provider decision-making model.

- Any patient with possible exposure to Zika virus who proceeds with attempting pregnancy after negative viral testing should be counseled about the possible presence of virus with a negative test (i.e., a false-negative result), the risks of subsequent infection in at-risk women, the possible viral effects on the fetus (e.g., congenital brain abnormalities), and testing during pregnancy as per national or regional guidance.

3. **Men who have confirmed Zika virus disease should wait at least 3 months after onset of illness to attempt reproduction.** For women with confirmed Zika disease, the CDC recommends waiting 8 weeks while the WHO suggests a more conservative approach of waiting 6 months to attempt pregnancy. The temporal relationship between the presence of viral RNA and infectivity is not known definitively and, thus, the absolute duration of time to wait before attempting pregnancy is unknown. In one study, semen samples were analyzed over time in one hundred eighty-four Zika virus positive men. Although the virus persisted in one sample up to 281 days, only 7% had detectable Zika virus RNA after 90 days (mean time for clearance was 54 days). Infectious Zika virus was detected by plaque assay in only 3 of 19 samples within 30 days, and in none of the samples collected past 30 days. Additionally, data available are increasingly supportive of an 8-week waiting period for women because viral persistence in blood is short for them and they do not appear to have any other immunologically protected sites.

- The decision to wait 8 weeks (CDC) vs. 6 months (WHO) for the woman and 3 vs. 6 months for men with Zika virus disease should be made using a shared patient-provider decision-making model taking into account any new available data and such variables as age of the female patient and other infertility factors with documentation of the conversation and decision.

4. **Symptomatic women and men attempting pregnancy through ART with possible Zika virus exposure should have testing** that includes the Zika virus nucleic acid test (NAT) to rule out active Zika infection, and serologic testing, as outlined in section #8 below, to identify Zika immunity, before proceeding on with infertility treatment. One must remember that men, however, may harbor Zika virus in semen after NAT testing in blood becomes negative. If testing is performed, attempting pregnancy should be considered only if NAT is negative. Otherwise, the couple should delay attempts at pregnancy using the same guidance of known infected individuals. Couples should understand that testing may be costly.

5. **Areas at increased risk for Zika virus transmission**

The CDC, in collaboration with FDA, has developed a process to define areas at increased risk for Zika virus transmission within the U.S. and throughout the world.

- **Within the U.S.**
  
  The US is the only country for which we have current, accurate information regarding Zika risk. There is no current local transmission of Zika virus in the continental United States as of February 28, 2019. This includes Florida and Texas, which last reported local transmission of Zika virus by mosquitoes in 2016-17. No Zika virus transmission by mosquitoes has ever been reported in Alaska and Hawaii.

  This information is subject to change. An up-to-date list of Zika virus transmission in the United states can be found at the CDC website: [https://www.cdc.gov/zika/geo/index.html](https://www.cdc.gov/zika/geo/index.html)

- **Outside the U.S.**
  
  For countries and territories outside the U.S. states, the CDC has created a [world map of areas with risk of Zika virus infection](https://www.cdc.gov/zika/geo/index.html), which will be updated on a regular basis. This map indicates the level of risk using four different color shading:

  Red: Country or territory with current Zika outbreak
  Purple: Country or territory with any prior or current reports of mosquito-borne Zika transmission
  Yellow: Country or territory with the vector and no reported mosquito-borne Zika transmission
  Green: Country or territory with no mosquitoes that spread Zika

  The CDC categorizes Red and Purple areas as those at increased risk of Zika virus transmission. Any country that reports an outbreak above baseline transmission will turn Red on the map, and the recommendation will be not
to travel there. The decision of whether or not to travel to a Purple country before conception is a function of patient risk tolerance.

- It should be noted that the US is the only Purple country in which there is no known current risk of Zika. The remaining Purple countries have reported past Zika transmission and might have current Zika transmission. The CDC surveillance system functions only in the US. Surveillance in most other countries is local, and the last reported date of ZIKA transmission can reflect a lack of testing or reporting rather than no recent ZIKA transmission. As a result, outside of the US the CDC cannot differentiate between past and current ZIKA risk.

6. **Asymptomatic women and men undergoing ART with possible exposure to Zika virus or who have traveled to a zone of possible Zika exposure** (see 5. Areas at increased risk for Zika virus transmission, above) **should wait 8 weeks for women and 3 months for men. Alternatively, they should consider testing for Zika infection**, the decision again being made using a shared patient-provider decision-making model. If testing is opted, it should begin with NAT and be followed by serology testing as outlined in section #8 below at or beyond 15 days from exposure by which time Zika IgM would be positive if infection occurred with the exposure. If testing is performed, attempting pregnancy should not be considered if NAT is positive. If immunity to Zika is inferred by either prior positive NAT or serology testing, future NAT testing is not needed for subsequent ART treatments.

7. **Women and men who reside in areas of active Zika virus transmission** (see 5. Areas at increased risk for Zika virus transmission, above) **should talk with their health care providers about attempting reproduction.**

- Patients desiring pregnancy should be counseled about the risks of infection during pregnancy and methods to avoid infection.
- Ideally, patients living in areas of active Zika transmission would delay attempts at pregnancy until the risk of infection during pregnancy is minimal.
- Asymptomatic women and men with ongoing Zika virus exposure who decide to undergo ART should be offered Zika virus testing (NAT), to avoid proceeding with a NAT-positive patient, and possibly serology testing to potentially identify Zika immune patients who can proceed with treatments avoiding subsequent NAT testing as long as 3 months has passed from best calculated infection for men and 8 weeks for women. If opted during a planned fresh cycle, this testing should be timed as close to the retrieval as is practical and at a time that will allow the review of results before the retrieval. Similarly, if opted in a planned thaw transfer cycle, the testing should be performed as close to the time of transfer as is practical and at a time that will allow the review of results before the transfer. As stated above, patients tested should understand the occurrence of false-negative and false-positive results and be reminded that infection can occur at any time after the testing.
- For males or females with a positive NAT result, treatment of infertility should be halted immediately. It should be deferred until 1) a subsequent NAT is negative on both the male and female and 2) at least 3 months have passed in the male and 8 weeks to 6 months have passed in the female from the time of the last positive result.

8. **Additional strategies may be considered for asymptomatic couples residing in a Zika area of active transmission undergoing ART treatment.**

- For males or females without testing, or with a negative NAT test result who are concerned that they have false negative testing or may become infected after testing, consideration can be given for gamete or embryo cryopreservation and quarantine until: 1) a subsequent NAT re-test is negative on both the male and female and 2) at least 8 weeks have passed from the time of the gamete collection.
- For males not previously infected with the Zika virus who are planning travel to an area of active virus transmission, consideration can be given to semen cryopreservation before travel. Ideally, they should be tested for Zika virus RNA at the time of semen collection and within 1 week after return.
- Both of these scenarios are predicated on the belief that the semen samples are free of Zika. There is no evidence that cryopreservation of sperm kills the virus, and recent evidence demonstrates that Zika may persist in washed semen samples.
Zika Testing
9. Testing for Zika presents challenges because of the variable availability of tests, the information provided by tests, and the interpretation of results. Testing is not universally available for use in those individuals for whom testing is recommended, and the cost is not universally covered by insurance.

- Symptomatic exposed patients and concerned at-risk patients should be referred to Infectious Disease (ID) specialists prior to attempting pregnancy. ID specialists will be aware of the Zika tests available in their community, the limitations and interpretation of the results of these tests, which patients will be allowed testing by these testing facilities, and whether testing is covered by insurance.
- At-risk patients should be counseled that Zika virus has been found in semen and cervical and vaginal secretions of infected individuals, and sexual transmission has been reported. However, Zika testing of semen and cervical and vaginal fluids is not currently recommended.
- A common testing paradigm for a symptomatic exposed individual begins with the Zika virus nucleic acid test (NAT). If the NAT is positive, a Zika diagnosis may be given realizing that false positive results can occur. If the NAT is negative in a symptomatic individual from a high prevalence area, Zika IgM testing is indicated.

SUMMARY TABLE. CDC recommendations for preconception counseling and prevention of sexual transmission of Zika virus among persons with possible Zika virus exposure — United States, August 2018

<table>
<thead>
<tr>
<th>Exposure scenario</th>
<th>Recommendations (update status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only the male partner travels to an area with risk for Zika virus transmission and couple planning to conceive</td>
<td>The couple should use condoms or abstain from sex for at least 3 months after the male partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (Recommendation updated 2018)</td>
</tr>
<tr>
<td>Only the female partner travels to an area with risk for Zika virus transmission and couple planning to conceive</td>
<td>The couple should use condoms or abstain from sex for at least 2 months (8 weeks) after the female partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (No change in recommendation)</td>
</tr>
<tr>
<td>Both partners travel to an area with risk for Zika virus transmission and couple planning to conceive</td>
<td>The couple should use condoms or abstain from sex for at least 3 months from the male partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (Recommendation updated 2018)</td>
</tr>
<tr>
<td>One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for Zika virus transmission) and couple planning to conceive</td>
<td>The couple should talk with their health care provider about their plans for pregnancy, their risk for Zika virus infection, the possible health effects of Zika virus infection on a baby, and ways to protect themselves from Zika. If either partner develops symptoms of Zika virus infection or tests positive for Zika virus infection, the couple should follow the suggested timeframes listed above before trying to conceive. (No change in recommendation)</td>
</tr>
<tr>
<td>Men with possible Zika virus exposure whose partner is pregnant</td>
<td>The couple should use condoms or abstain from sex for the duration of the pregnancy. (No change in recommendation)</td>
</tr>
</tbody>
</table>

Source: Polen, KD, et al. e

Fertility Treatments Using Autologous or Donated Gametes
10. Fertility treatment for sexually intimate couples using their own gametes and embryos should follow the timing recommendations for persons attempting reproduction.

11. The Food and Drug Administration (FDA) guidance remains unchanged in the May 2018 update, stating that living donors of human cells, tissues, and cellular and tissue-based products (including sperm, oocytes, and embryos) should be considered ineligible for donation if they have any of the following risk factors:

- Medical diagnosis of Zika virus infection in the past 6 months
- Residence in or travel to an area with an increased risk of Zika virus transmission within the past 6 months
- Sex within the past 6 months with a person who has either of the risk factors listed in items 1 or 2, above

12. Directed (or known) donors must undergo the same evaluation and eligibility determination as anonymous donors.
13. Fertility treatment using a gestational carrier should follow timing recommendations for gestational carriers as for persons attempting reproduction.

14. When using donated embryos, consideration should be given concerning the potential exposure of the embryos to Zika virus, particularly if the embryos were frozen at a time of active Zika transmission and before screening processes were in effect.

15. It is tempting to assume that the use of techniques for sperm preparation that have been shown to be effective for minimizing the risk of HIV transmission should be similarly effective for minimizing risk of Zika virus transmission. However, these procedures have not yet been demonstrated to be effective in preventing transmission of the Zika virus nor has cryopreservation been demonstrated to destroy the Zika virus. In a recent publication, motile sperm obtained after sperm washing were found to have Zika virus RNA in 3 of 14 patients at day 7 and, by day 20, 4 of 15 patients.\(^m\)

16. Data involving Zika, its transmission and infectivity, and its adverse effects on fetuses and adults is changing daily. Guidance based on current knowledge will most likely continue to change as our understanding of this virus rapidly changes. Any guidance published today may not be accurate for counseling and treatment of individuals tomorrow. Refer to the CDC Zika website for the most updated information: https://www.cdc.gov/zika/.\(^n\)

17. It is suggested that, until more data are available about asymptomatic males and females potentially exposed to Zika, practitioners providing treatment involving gametes to potentially infected individuals should include language in their consent forms that conveys this gap in knowledge.

References


\(^f\) Centers for Disease Control and Prevention Areas at increased risk for Zika virus transmission through blood or tissue donation in U.S. states. Available at: https://www.cdc.gov/zika/areasatrisk.html. Accessed July 16, 2019.


This report was developed under the direction of the Zika Virus Guidance Task Force* of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Executive Committee of the American Society for Reproductive Medicine has approved this report.

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